PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Peter DROGE, Nicole CHRIST and
Elke LORBACH

Serial No.: 10/082,772

Filed: February 22, 2002

For: SEQUENCE-SPECIFIC DNA RECOMBINATION IN EUKARYOTIC CELLS

Group Art Unit: 1636

Examiner: Q. Nguyen

Atty. Dkt. No.: DEBE:008US/SLH

CERTIFICATE OF ELECTRONIC SUBMISSION

DATE OF SUBMISSION: October 4, 2006

DECLARATION OF PETER DRÖGE UNDER 37 C.F.R. §1.132

I, Dr. Peter Dröge, do declare that:

1. I am a citizen of Germany residing in Singapore. I currently hold the position of Associate Professor and Head of Division at the School of Biological Sciences, Nanyang Technological University, Singapore. My research experience includes genetic modification technologies and molecular genetics. A copy of my *curriculum vitae* is attached.

2. I have reviewed the above-captioned application, a copy of the pending claims, and the Office Action mailed on May 4, 2006, as well as the literature cited therein. I understand that the examiner in charge of the present application asserts that one of ordinary skill in the art would find the present invention "obvious" over the citations of Hartley and Christ & Dröge, and Crouzet and Christ & Dröge, optionally in view of Capecchi. For the following reasons, I respectfully disagree.

3. The Int-h/218 mutant was originally generated with an aim to design a recombinase which exhibits an increased binding affinity for so-called core binding sites. The latter are present in all *att* sites (the recombination substrates). This enzyme (and the parental mutant Int-h) has never been studied in detail *in vitro*, *i.e.*, purified and analyzed with DNA substrates in the test tube. It was, therefore, not clear whether the enzyme would be active in the absence of protein co-factors and negative DNA supercoiling of substrate DNA. However, both factors are present in *E. coli*. Before we transferred this mutant to mammalian cells, we knew that the enzyme could catalyze an abnormal reaction in *E. coli* in the absence of the co-factor IHF (Christ and Dröge, 1999). However, one has to realize that DNA substrates (whether episomal or genomic) are negatively supercoiled inside *E. coli*. It was, therefore, not obvious to one of ordinary skill to deduce from the existing data that the mutant recombinase would work inside mammalian cells where the DNA is topologically relaxed. In fact, up to this day, the reason why both Int-h and the double mutant Int-h/218 are functional in eukaryotic cells remains a mystery. One possibility is that there is an unidentified mammalian co-factor which supports the prokaryotic recombinase. Based on these facts, a claim that the invention is "obvious" reflects a thorough misunderstanding of the topic.

4. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this patent, and any reexamination certificate issuing thereon.

Sep. 29th, 2006
Date

Dr. Peter Dröge

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